in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains separately and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains in functional form concomittantly.

30. (Three Times Amended) A mammary gland epithelial cell comprising the construct of claim 28 and a construct comprising an immunoglobulin protein-coding sequence which encodes a light chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains separately and secretes a heterologous, assembled immunoglobin comprising the light and heavy chains in functional form concomittantly; and,

wherein said promoter sequence is selected from a group consisting of: beta lactoglobulin promoter, whey acid protein promoter, and the lactalbumin promoter.

Please also see a Claims Appendix with a complete listing of the claims as amended without correction marks.

REMARKS

The Office Action of September 10, 2003 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for her thorough and detailed remarks. Claims 19, 21-22 and 25-30 are currently pending. Claims 19, 29 and 30 are amended herein. Claim 23 is canceled herein. No claims have been added herein.

Claim Objection

Applicants thank the Examiner for acknowledging the effectiveness of the previous remarks regarding claims 29 and 30 in the last response received from the Applicant causing the withdrawal of the prior objections by the Examiner's prior objection to the specification.

With specific regard to claims number 19, 22 and 25-28 however, applicants believe that the objection has been rendered moot by the amendments made herein to claims 19, 29-30. Reconsideration is respectfully requested.

AMENDMENTS AFTER FINAL REJECTION

This response to the Examiners Final Rejection includes within it amendments to the claims. Amendments such as these can be included within a response to such a Final Rejection if such amendments are made for good and sufficient reasons, as laid out by CFR § 1.116. Justifications for such amendments include: 1) the Applicant's attempt to answer new issues or rejections raised by the Examiner; 2) the amendments reduce the issues to be considered in an appeal; and/or 3) the amendments leave the application in better condition for allowance.

In this instance all possible efforts have been put forward to remove all of the Examiners' rejections to the remaining claims. The pending claims, as amended and provided by Applicant herein, are thus intended to be both part of a fully responsive reply to the Examiner's remaining rejections and fully grounded in the teachings of the specification. MPEP §§ 608.01; 714.

The Applicant believes that the amendments which have been made, along with the nature of this response serve to put all the remaining claims in condition for allowance.

Given the above, it is specifically and respectfully requested that the Examiner allow the amendments after final, made herein.

The Rejections Under 35 U.S.C. §103(a)

A. Meade et al.,and DeBoer et al.,

Claims 19, 22 and 25-28 remain rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., reference (U.S. Patent No.# 4,873,316)(hereinafter the '316 patent) and the

DeBoer et al., citation (U.S. Patent No.# 5,633,076)(hereinafter the '076 patent). The rejection of the claims, as amended, is respectfully traversed.

As previously stated by the Applicant the prior establishment of a *prima facie* case of obviousness is the procedural tool required by the MPEP for allocating the burden of proof as between an Applicant and the Examiner. That is, the initial burden must be met by the Examiner in her presentation of a *prima facie* case of obviousness that, without impermissible novelty, can objectively be shown to negative patentability. Respectfully, in the current case the Examiner has failed to meet this burden and establish the required case of obviousness. Therefore, and without more, the claims are not rendered obvious and should go to issue. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir.1992).

It is important to note that a *prima facie* case of obviousness is only established when the teachings from the prior art itself can be said to quantifiably suggest the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993); In re Rijckaert, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993).

The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

(1) the claimed invention must be considered as a whole;

(2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(4) reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); *In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In addition, it must be respectfully reiterated that the citations provided by the Examiner fail, when taken as a whole as

required by MPEP § 2141, to recognize, expressly or implicitly, any need, possibility or benefit of combining their disparate teachings in such a way that they might then read on the instant claims. Therefore, and as pointed out below, they are objectively incapable of supporting or maintaining an obviousness rejection under § 103(a). Carella v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

It is also important to point out that obviousness is not established unless the teachings of the prior art would have suggested the claimed subject matter to a person of ordinary skill in the art with a reasonable likelihood of success of achieving the suggested invention. In re Dow Chem., 5 USPQ2d 1529, 1531 (1988). Any motivation or suggestion to modify the prior art references must flow from some relevant teaching in art that is relatively analogous as to the desirability or incentive to make the modification needed to arrive at the claimed invention. In re Napier, 55 F.3rd 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995); In re Gorman, 933 F.2d 982, 986-87, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

B. Meade et al.,

The Meade et al, patent provides some insight and teachings in the use of DNA constructs and in the development of transgenic animals for the production of biopharmaceuticals in milk. However, the teachings of Meade et al., do not by themselves or in combination with any of the other cited art render the instant claims obvious.

It must be stated that claims 19, 22 and 25-28 are directed to DNA constructs for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. The construct of the invention includes an appropriate promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence of interest is inserted into the restriction site. Claims 29 and 30 are directed to a mammary epithelial cell and mammary gland which will act to express these immunoglobulin constructs, and a second construct encoding the opposite immunoglobulin chain (i.e., the heavy or light chain, respectively) for expression.

More to the point for the immediated claims is that the prior art Meade et al., patent fails to provide or teach the following:

I. Meade et al. fails to teach or suggest that expressing the light chain and heavy chain of an immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors, one encoding the heavy chain and one encoding the light chain. Meade et al., simply fails to contemplate expressing these chains separately;

II. Meade et al., fails to teach a separate construct for the light chain and the heavy chain for the production of a single immunoglobulin species;

III. Meade et al, fails to indicate that the use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk;

IV. Meade et al., fails to disclose a unique restriction between the promoter and the 3' non-coding sequence, wherein the immunoglobulin coding sequence is inserted into the restriction site;

V. Meade et al. fails to teach that the claimed construct should have a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted; and,

VI. Meade et al., fails to teach the unique construction of the restriction site – such that it has a coding sequence inserted into the site- that then allows for a vector which can easily be modified, without the need for cleaving the remaining construct to insert various immunoglobulin chains is an improvement over the prior art. This construction allows for easier expression of a variety of different immunoglobulin coding sequences. Thus, the use a unique restriction site into which the immunoglobulin coding sequence is inserted, adapts to the unique features of expressing immunoglobulins.

This lack of guidance, that is, the lack of anything "teaching" the invention is clear on a basic level and more concretely is clear with objective elements I through VI as provided above.

Given this, and the controlling precedent cited above, the cited are simply fails to render the instant invention obvious. Reconsideration of the rejected claims is respectfully requested.

C. DeBoer et al,

DeBoer et al., does not provide what Meade lacks, see "I" through "VI" above. Importantly, neither Meade et al. nor DeBoer et al. teach or suggest the claimed construct having a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted. DeBoer also fails with regard to each and every other element called out above as deficient in Meade et al. Respectfully, the lack of even one element I – VI as provided above is sufficient to prevent an obviousness rejection from being maintained.

Respectfully, and to clarify the Applicants position DeBoer et al. does not make up for any of the other deficiencies of the Meade et al. reference. Specifically, the Applicants understand the assertion of the Examiner that DeBoer et al., at Column 30 lines 45-50 and Figure 7E provides for the development of a construct having a casein promoter and a 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and the 3' coding sequence. Applicants must reiterate, however, that neither the textual citation of DeBoer or the Figure relied upon by the Examiner demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted, this understanding is fundamental to the current invention. As already stated, DeBoer presents the state of the art as of its filing date but does not teach the invention as presented by Applicants. That is, it simply does not present the elements of the current invention regarding the production fully-functional, fully-assembled immunoglobulins in transgenic mammalian milk. It does not attempt to teach this modification of the prior art. Moreover, it does not teach any combination with Meade et al.

Thus, amended independent claim 19, which recites elements not rendered obvious by Meade or DeBoer alone or in combination, cannot be obvious as against either of these references. Therefore, the Examiner's rejections are traversed and reconsideration is respectfully requested. Reconsideration is respectfully requested.

Dependent claims 22, and 25-28 being dependent upon and further limiting independent amended claim 19 should also be allowable for those reasons, as well as for the additional

recitations they contain. Applicants respectfully request reconsideration of the rejection of claims 19, 22 and 25-28 under 35 U.S.C. § 103(a) in view of the above amendments and remarks.

No Objectively Quantifiable "Suggestion" of Desirability of Combination

When determining the patentability of a claimed invention which combines two known processes or elements, a key question of allowability is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984).

That is, the art **must** at least indicate that a combination would be possible and desirable in order to render a future combination of that art obvious to one skilled in the relevant field. Before obviousness may be established, the examiner must show that there is either a suggestion in the art to produce the claimed invention or a compelling motivation based on sound scientific principles. Respectfully, logic compels that the suggestion or motivation be accompanied by a general knowledge of the existence of art recognized techniques for carrying out the proposed invention and that the proposed solution be extant in relevant fields of endeavor such that a reasonable worker in the field would look to them as a source or insight or solutions to existing problems or limitations in the art.. Ex parte Kranz, 19 USPQ2d 1216, at 1217-1218 (1990). *See also*, Ex parte Levengood, 28 USPQ2d 1300, 1301, (Bd. Pat. App. & Int. 1993).

As respectfully provided above there are substantial limitations preventing either Meade or DeBoer, together or alone, from successfully rendering the instant claims obvious. However, they also fail to quantifiably suggest the claimed subject matter to a person of ordinary skill in the art.

It is well accepted that references cannot be combined without some suggestion in the references themselves that such combination may be made. How, then, can the disclosure of a single reference, here Meade et al., be taken to support an allegation of obviousness in the absence not only of any teaching within the reference concerning the individual features alleged to be obvious, but also in the absence of any other reference, here DeBoer et al., showing these

features? The answer is that it cannot. The art presented by the Examiner simply does not accomplish the task.

According to In re Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992), the Examiner may not suggest modifying the references using the present invention as template absent a suggestion of the desirability of the modification and combination in the cited art. No such call for combination is present. Simply piecing together the prior art does not a *prima facie* case of obviousness make. In re Wright 848 F.2d 1216, 6 U.S.P.Q. 2d 1959 (Fed. Cir. 1988). As such, reversal of the instant rejection is respectfully requested.

D. Vandamme et al.,

Amended claims 29 and 30 remain rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., DeBoer et al., references in view of Vandamme et al. This rejection is, respectfully, improper, and should be reversed.

The limitations of the DeBoer et al., and Meade et al., citations are provided above. Moreover, with regard to claims 29 and 30 the Examiner notes that these citations "do not teach a mammary gland epithelial cell comprising two separate vectors encoding the heavy chain and light chain of the immunoglobulin" (Office Action of 12/17/02 page 5, 2nd paragraph). In addition, they do not add "expressing such chains separately...concomitantly."

Vandame et al., does not and cannot make-up for these deficiencies. As pointed out below the Vandamme citation is non-analagous art and unavailable for combination with the prior cited art to render obvious the instant claims. Moreover, Vandamme too lacks any suggestion to combine with Meade or DeBoer.

Applicant must again respectfully point out that the Examiner does not provide any support to support her suggestion that the Vandamme *et al.*, an *in vitro* cell culture system, could in any manner, fashion or design serve as an accurate approximation of functional mammary gland in a whole animal. The mammary organ is an exceptionally complex tissue that produces a very complex mixture known as milk. This process is initiated only in mammary epithelial cells in response to a specific order and cascade of hormones within the adult female mammal. The instant invention provides for using that process through the manipulation of various cell

populations to produce a fully-assembled, fully-functional immunoglobulin of exogenous origin not otherwise found in milk.

In fact, any teaching that proposes the use of *in vitro* expression methods as optimal is in essence teaching away from the whole animal transgenic model & platform of the Applicants. Thus, in addition to being non-analogous art any teachings to those in the field would be to teach away from the approach reached by Applicants. Therefore, the Examiner's analysis thus inappropriately bases its rejection on the use of Vandamme et al., on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target protein or protein fragment is much like another, and that therefore any cellular expression system with any given target protein is an appropriate and analogous prior art reference for the claimed invention of another such expression system. However, as the Federal Circuit has stated, "[t]wo criteria are relevant in determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the art is not within the same field of endeavor, whether it is still reasonably pertinent to a particular problem to be solved," Wang Laboratories, Inc. v. Toshiba Corp. 26 U.S.P.Q. 2d 1767, 1773 (Fed. Cir. 1993); *see also,* In re Clay, 23 U.S.P.Q. 2d 1058, 1060 (Fed. Cir. 1992); (*Wang* is cited here for the proposition above of legal analysis not specifically for the narrow elements of the case). The Court further let stand a lower Court finding in Wang that the prior art reference was not analogous art and was not reasonably pertinent, i.e. the art would not logically have commended itself to an inventor's attention in considering his problem. Wang at 1773, and Clay at 1061. It must be reitereated that the relevance of the Wang analysis to the instant matter lies in the fact that the Vandamme reference is silent with regard to:

a. whole animal systems;
b. the physiological effect of lactation hormones;
c. milk promoters; and
d. focuses and provides teaching with regard only to comparatively simple in vitro expression systems.

These fundamental differences are simply not overcome and lead to an objective conclusion that the respective fields of science are non-analagous with there diverse methods, processes and goals for increased production of a given molecule of interest. The problems are

different as are the solutions. More important, no one in the prior art established an *in vitro* system where the efficiency of synthesis of milk component proteins, including exogenous immunoglobulins of interest, even approximate those found *in vivo.*

More to the point, to those of ordinary skill in the art it, at the time of the present invention, it would appear that Vandamme et al., taught a difference between the *in vitro* cell culture of mammary cells, and the behavior of these same cells at the whole animal level. The consideration of Vandamme et al., cannot be done in a vacuum, the art must be considered as a whole. From this perspective the art taught away from the combination of Vandamme et al., with Meade et al., and/or DeBoer et al. These references are directly contradictory, such that one skilled in the art would not expect that Vandamme et al., would be used, compared, or would correspond to the results seen in the whole animal, or that the two studies could be combined.

Lactation is a hormonally induced condition that relies on the whole animal physiological interaction with a variety of hormones, simply to be initiated. Once milk synthesis is begun, there are considerable changes in cell morphology and metabolism not duplicated, taught, or implied by Vandamme's *in vitro* cultures. Moreover, multiple hormonal interactions not supplied by Vandamme are needed to maintain the lactating state and produce a protein of interest. Vandamme simply is not experimenting on the same or even a similar system, and thus cannot render that system or its discoveries obvious. Whole animal experiments involve the incredibly complex web of physiologic interactions **never** approximated by cell culture research. Prolactin, insulin and hydrocortisone are the minimal hormone mix needed to induce mammary cell differentiation and cause inactive cells to become active, but use of them in a vacuum or in an isolated culture dish does not and cannot approximate the effects on an whole animal. Thus, there is no *in vitro* system to study regulation of milk synthesis in active cells. The claims relate to established lactation in a whole animal and demonstrate elevated milk protein synthesis in the whole animal. More to the point Vandamme is simply not available for combination with any whole animal transgenic system of the type provided by Applicants.

Given the above, no obviousness rejection can be maintained based on the Vandamme *et al.,* reference. Therefore, any rejections of the claims at issue here under § 103 should be reversed, and such is respectfully requested.

Vandamme as Non Analagous Art

More broadly no artisan has established and maintained such an *in vitro* system. Simply put, the claims as a whole, and claims 29 and 30 specifically, recite the use of the whole animal, the Examiner attempts to apply *in vitro* cell culture data as an approximation of this whole animal system sufficient to render obvious the work of the Applicants. The two systems are simply incompatible, it cannot be understated that they represent to very different and very distinct approaches to the production of biologics and biopharmaceuticals in an academic and industrial sense. **They simply are not now and have never been predictive of each other, therefore they are clearly non-analogous art unavailable for any combination**. That is Vandamme et al., teaches in an entirely different field of endeavor than that present invention or the Meade or DeBoer citations. It must be remembered that an inventor is not expected to be skilled in every branch of technology, science, and human knowledge, as was stated in In re Wood, "An inventor [can] not possibly by aware of every teaching in every art." In re Wood, 599 F.2d 1032, at 1036 (CCPA 1979). The comparison of the current invention and Vandamme is thus starkly different. Moreover, the Vandamme reference also fails to be reasonably pertinent to the problem with which Applicant is concerned. A reference that can considered reasonably pertinent is one that though it may be in a different field from that of the inventor's endeavor, is one which because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering the problem at hand. Thus, the purposes of both the invention and the prior art are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to resolve. In re Clay, 966 F.2d 656, at 659 (Fed. Cir. 1992); *accord*, In re Oetiker. In the current invention the Applicant sought to develop a method of expressing immunoglobulins in transgenic mammals while Vandamme seeks to use an *in vitro* system for expression. Applicant respectfully submits therefore that, as in Clay and Oetiker, the Vandamme reference is not within the field of applicant's endeavor, and is not reasonably pertinent to the particular problem with which the present invention is concerned because it has not been shown that a person of ordinary skill, seeking to solve a problem in a transgenic animal, would reasonably be expected or motivated to look to at the in vitro cell culture techniques of Vandamme et al., to solve the problem. Respectfully, the concerns for expression of immunoglobulin proteins and their assembly is an entirely different problem, with an

entirely different set of concerns and hurdles preventing success than those inherent in the instant invention. Thus, though Vandamme might target the production of a similar protein as those provided in the instant specification, the problem addressed and the solution provided by Vandamme et al., have little or nothing to do with the myriad of expression problems overcome by the instant claims, therefore falling outside the scope of appropriate art.

In a similar situation, the Federal Circuit concluded that as between a method and apparatus in which film is transferred to a welding station and a tape splicing machine capable of handling the same film, "[in] the light of all this evidence, one can reasonably conclude that the reference is not within the field of this inventor's endeavor and was not directly pertinent to a particular problem with which the inventor was involved." King Instrument Corp. v. Otari Corp., 226 U.S.P.Q. 402, 405 (Fed. Cir. 1985); *see also,* Union Carbide Corp. v. American Can Co., 220 U.S.P.Q. 584, 588 (Fed. Cir. 1984).

As in the King and Wang situations, the instant claimed invention is directed to features, methods and solutions of problems which are alien and non-analogous to the prior art cited by the Examiner. Therefore the teachings of Vandamme *et al.*, are not pertinent to the claimed invention.

Accordingly, as in *Wang* and *King,* one must conclude that Vandamme *et al.* is not within the field of this inventor's endeavor and is not pertinent in any way to the particular problems solved by the invention as provided in claims or available for use in maintaining an obviousness rejection.

E. Buhler et al., Bishoff et al., Gordon et al., Ebert et al., and Stinnakre et al.,

Claims 19, 21-22 and 25-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., DeBoer et al., references when taken in view of Buhler et al., Bishoff et al., Gordon et al., Ebert et al., and Stinnakre et al.,

As stated in a prior Response, the citations cited immediately above do not teach or suggest the claimed invention. Rather Bischoff et al., Buhler et al., Gordon et al., Ebert et al, and Stinnakre et al. are merely relied upon by the Examiner for their disclosure of specific milk protein promoters, namely whey acid promoter and lactalbumin promoter and none of these references make up for the deficiencies of Meade et al. and DeBoer et al., outlined above. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Respectfully, the Examiner must provide more than an odd collection of references that recast pieces of known technology, and other elements that may hint at the novelty created by the Applicants in the instant invention. The Examiner must provide references that ***knowingly*** suggest the combination of protocols, tests, or principles, which will lead to the invention to be rendered obvious, and read upon its claims. The Examiner has not provided these references. Rather the Examiner has stated that the instant claims are obvious "to one of ordinary skill" (Office Action of December 17, 2002, page 6, last paragraph). Without more, this is a classic reproduction of the invention from improper hindsight, which cannot be used to negative patentability or establish the required case of *prima facie* obviousness. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

The important point here is that with regard to the above rejections under 35 U.S.C. §103(a), it should be pointed out that to support the combination of various sources to create an obviousness rejection those sources must themselves specifically contain or objectively suggest to the skilled artisan a combination of art to achieve the invention – this they do not do. To allow anything less would be to render 35 U.S.C. §103(a) a subjective measure of patentability without any parameters or objective standards. This is what the Federal Circuit has squarely decided against in its statements about the improper application of hindsight to sustain an obviousness rejection. In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990)(*en banc*); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

It should be noted that in response to the Examiner's very thorough comments that existing independent claims 19, 29 and 30 have been amended herein to address a variety of the Examiner's concerns. Therefore Applicant requests reconsideration of the claims in light of these amendments and claim additions. Given the analysis above, the Examiner's remaining objections to the claims as amended are respectfully traversed. Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection. Applicants therefore respectfully request the withdrawal of the Rejection of amended claims 19, 21-22 and 25-28 under 35 U.S.C. §103(a). Reconsideration is respectfully requested.

Other than a fee for the appropriate extension of time no fee is deemed necessary in connection with the filing of this Amendment. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 3/10/04

By:

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Claim Appendix on next page

IN THE CLAIMS:

19. (Twice Amended) A DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal comprising a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site; and wherein said DNA construct is integrated into the genome of said mammal in such a way that said protein-coding sequence is expressed in the mammary gland of said mammal and secreted from said mammary gland in the milk of said mammal; and,

wherein immunoglobulin is primarily or completely of human origin

21. The construct of claim 19 wherein said promoter is selected from the group consisting of the beta lactoglobulin promoter, whey acid protein promoter, and the lactalbumin promoter.

22. The construct of claim 19 wherein said immunoglobulin protein-coding sequence encodes a light chain or a fragment thereof.

25. The construct of claim 19 wherein said promoter is the casein promoter.

26. The construct of claim 19, wherein the restriction site is an XhoI restriction site.

27. The construct of claim 19, wherein the 3' non-coding sequence is a 3' non-coding region from a mammary-specific gene.

28. The construct of claim 19, wherein the immunoglobulin protein-coding sequence encodes a heavy chain or a fragment thereof.

29. (Amended) A mammary gland epithelial cell comprising the construct of claim 22 and a construct comprising an immunoglobulin protein-coding sequence which encodes a heavy chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains separately and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains in functional form concomittantly.

30. (Three Times Amended) A mammary gland epithelial cell comprising the construct of claim 28 and a construct comprising an immunoglobulin protein-coding sequence which encodes a light chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains separately and secretes a heterologous, assembled immunoglobin comprising the light and heavy chains in functional form concomittantly; and,

wherein said promoter sequence is selected from a group consisting of: beta lactoglobulin promoter, whey acid protein promoter, and the lactalbumin promoter.